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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/917,858	07/31/2001	Regina Geertruida Schoemaker	147/50194	9455

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EXAMINER
CHANNAVAJJALA, LAKSHMI SARADA

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 11/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	licant(s)	
	09/917,858	SCHOEMAKER, REGINA GEERTRUIDA	
	Examiner	Art Unit	
	Lakshmi S Channavajjala	1615	

-- Th MAILING DATE of this communication appears on th cover sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt of request for extension of time and amendment B, both dated 9-9-02 is acknowledged. Claims 1-5 are pending.

Claims

Instant claims 1-5 are directed to a method of treating a patient who has suffered a myocardial infarction, comprising administering 4-chloro-5-[(4,5-dihydro-1H-imidazol-2-yl)-amino]-6-methoxy-2-methylpyrimidine, effective to inhibit or treat myocardial damage secondary to myocardial infarction, for postmyocardial infarction management and promoting recovery or rehabilitation of myocardial status.

The following rejection has been maintained for the reasons of record:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/46241 (submitted on PTO-1449, referred to as WO '241).

WO '241 discloses a method of treating congestive heart failure by administering moxonidine (abstract, page 1, lines 10-15, page 13, lines 1-13, page 18, lines 14-22, page 19, lines 12-24). Examiner notes that the compound of the instant claims is also known as moxonidine (as described on page 1 of the specification). WO '241 disclose that moxonidine, a well tolerated anti-hypertensive drug (page 8, lines 16-29), reduces blood pressure and induce

regression of left ventricular hypertrophy (page 9, lines 30 through page 10, lines). WO '241 further discloses that moxonidine treatment reduces vascular resistance while increasing cardiac output (page 10, lines 24-29).

WO '241 does not explicitly state postmyocardial infarction or recovery of myocardial status, as claimed. However, WO '241 discloses that congestive heart failure (CHF) is the end result of long-term or severe cardiac deficits, often caused by long-standing hypertension, acute myocardial infarction, idiopathic cardiomyopathy and a wide variety of secondary insults (page 1, lines 22-26). Further, WO '241 disclose that cardiac and peripheral regulatory mechanisms such as increased heart rate, hypertrophy, increased sympathetic nervous stimulation etc., play a role early in CHF, which further contributes to myocyte necrosis, hypertrophy leading to increased myocardial remodeling and heart failure (page 1, lines 29 through page 3, line 36 and page 4, lines12-14). Examiner notes that same regulatory mechanisms are also observed in postmyocardial infarction patients (pages 3-5 of the instant application) as those described by WO '241. Therefore, moxonidine treatment of CHF taught by WO '241 reads on the instant treatment of postmyocardial infarction or myocardial damage secondary to myocardial infarction.

2. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Lepran et al (J. cardiovascular Pharmacology, 1994, submitted on PTO-1449).

Lepran et al disclose that increased sympathomimetic activity seen during the acute phase of myocardial infarction aggravates arrhythmias, frequently leading to life threatening ventricular fibrillation (Introduction on page S9). Lepran et al studied the effect of moxonidine

on arrhythmias induced by myocardial infarction in rats and observed that moxonidine significantly decreases the incidence of ventricular tachycardia during the first 15 minutes of infarction, decreased the infarct size and the number of animals survived without developing any arrhythmias was significantly increased (page S11, col. 2). Lepran et al further disclose that moxonidine at 0.03 mg/kg and 0.1 mg/kg is also effective in preventing reperfusion-induced arrhythmias after myocardiac ischemia (S11, col. 2).

Lepran et al does not explicitly state "postmyocardial management or recovery or rehabilitation". However, Lepran et al clearly state that arrhythmias and life-threatening ventricular fibrillation are caused due to increased sympathomimetic activity during the acute phase of myocardial infarction. In other words, Lepran et al aims at arrhythmias occurred after myocardial infarction. Therefore, it is implicit in the teachings of Lepran et al that moxonidine is administered to treat or inhibit the damage (arrhythmias or ventricular fibrillation) resulting from myocardial infarction (i.e., secondary to myocardial infarction or postmyocardial infarction). Lepran et al teaches that moxonidine is dissolved in saline, which reads on the instant carrier (claim 5). Examiner notes that instant application describes that moxonidine treatment is suitable to man and large animals (page 2, last paragraph) and experiments were performed on rats (pages 7-13). Accordingly, the instant term "patients" encompass rats, which are also used in the experiments of Lepran et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 97/46241 (submitted on PTO-1449, referred to as WO '241).

Instant claims are directed to a method treating a patient who has suffered a myocardial infarction by administering moxonidine effective for inhibiting/treating the secondary damage to myocardial infarction, effective to recover myocardial status and postmyocardial management.

WO '241 as described above teaches treatment of congestive heart failure (CHF) with moxonidine. WO '241 does not clearly state that moxonidine is used in amounts effective for postmyocardial management or for recovering myocardial status. However, WO '241 describes that congestive heart failure is a results of long standing hypertension, acute myocardial infarction etc., and also describes the same cardiac and peripheral regulatory mechanisms during CHF (page 1, lines 29 through page 3, line 36 and page 4, lines12-14), such as those occurring after myocardial infarction (as described by applicants on pages 3-5). Further, WO '241 shows that moxonidine induces regression of myocardial hypertrophy, which often proceeds heart failure, by decreasing blood pressure and reducing the thickness of left ventricular septal thickness (paragraph bridging pages 8 and 9) and increases cardiac output by reducing vascular resistance (page 10, lines 24-29).

Therefore, it would have been obvious for one of an ordinary skill at the time of the instant invention that moxonidine treatment taught by WO '241 would be effective in inhibiting or treating the damages secondary to myocardial infarction, in postmyocardial management and in recovering myocardial status because WO '241 teaches that conditions such as congestive

heart failure and myocardial hypertrophy occur after myocardial infarction i.e., secondary damage or postmyocardial condition. Therefore, one of an ordinary skill in the art would have administered moxonidine to patients suffered from myocardial infarction with an expectation to treat or manage the conditions after myocardial infarction such as heart failure, myocardial hypertrophy due to reduced hypertension, regressed ventricular septal thickness and increased cardiac output i.e., recovering myocardial condition.

Response to Arguments

Applicant's arguments filed 9-9-02 have been fully considered but they are not persuasive.

WO '241

Applicants argue that WO '241 fails to anticipate the instant claims because '241 application is limited to the use of moxonidine in the form of a "non-immediate relelase" composition for the treatment of congestive heart failure and only refers to hemodynamic parameters, which is not the focus of the claimed invention. Applicants also argue that significantly, patients suffering from myocardial infarction or from myocarditis were excluded from the study of WO '241, which alone refutes any assertion of anticipation or obviousness of instant claims. However, this argument is persuasive because instant claims are directed to treating a patient "who has suffered a myocardial infarction", effective to inhibit the myocardial damage secondary to myocardial infarction. In other words, the events or conditions subsequent to myocardial infarction, which cause further myocardial damage. Claims do not specifically state any particular event. Further, WO '241 states that CHF is caused by long term acute myocardial infarction (MI) and the patients excluded are those who had such in the 90 days

period previous to the trial. Accordingly, only the short-term MI patients are excluded by WO '241, but not all MI patients. Whereas '241 teach congestive heart failure (CHF) is one of the conditions, which is caused due to long-standing acute myocardial infarction. Thus, WO '241 teaches a post-myocardial condition. Further, WO '241 also states a chronic CHF leads to activation of neurohormonal systems, which leads to increased cardiac rate, myocyte necrosis and hypertrophy, which in turn leads to myocardial remodeling. Thus, WO '241 clearly aims at all the events that are post-myocardial infarction, which include secondary myocardial damage. Although applicants have argued that WO '241 only teaches hemodynamic changes, the reference does teach how these are further linked to increased cardiac rate, myocyte necrosis and hypertrophy i.e., myocardial conditions. Applicants have not shown how these hemodynamic conditions are distinct from the claimed conditions. With respect to the argument that the clinical trials did not include patients with myocardial infarction, WO '241 includes CHF patients in their trials and states that CHF is a result of long standing myocardial infarction. Accordingly, CHF patients of WO '241 belong to the claimed category of "patients who suffered myocardial infarction". With respect to the dosage, WO '241 also states an amount effective to diminish or relieve one or more conditions associated with CHF, thus, including the myocardial conditions.

Lepran:

Applicants argue that Lepran article is limited to describing the effects of moxonidine on arrhythmias induced by myocardial ischemia or reperfusion in an animal model and argues that article, similar to WO '241, focus on the hemodynamic characteristics. However, instant post-myocardial conditions do not distinguish from the conditions of Lepran. Applicants argue that the results regarding the dosages are contradictory and the claimed damage is distinct from

arrhythmia of the Lepran. However, applicants did not explain how they are different. Whereas, Lepran clearly states that moxonidine effectively reduces the arrhythmia caused by acute myocardial infarction. Applicants argue that the data in the instant application shows the damage to heart tissue (interstitial collagen, heart weight, hypertrophy) etc. However, instant claims did not limit to any of these myocardial damages tested by applicants, and instead are broad in scope such that they include the conditions of Lepran.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S Channavajjala whose telephone number is 703-308-2438. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-308-7924 for regular communications and 703-308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Lakshmi S Channavajjala
Examiner
Art Unit 1615

November 8, 2002

THURMAN K. PAGE
SUPERVISORY PATENT EXAMINER
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